UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/678,650	10/06/2003	Regine Hakenbeck	012627-037	7623

21839 7590 12/14/2007
BUCHANAN, INGERSOLL & ROONEY PC
POST OFFICE BOX 1404
ALEXANDRIA, VA 22313-1404

EXAMINER	
WILDER, CYNTHIA B	
ART UNIT	**PAPER NUMBER**
1637	

NOTIFICATION DATE	DELIVERY MODE
12/14/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

ADIPFDD@bipc.com
debra.hawkins@bipc.com

Office Action Summary	Application No.	Applicant(s)	
	10/678,650	HAKENBECK, REGINE	
	Examiner	Art Unit	
	Cynthia B. Wilder, Ph.D.	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 September 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) *15-27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,6-12,14 and 18* is/are rejected.

7)☒ Claim(s) *4,5 and 13* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/20/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

FINAL ACTION

1. Applicant's amendment filed September 20, 2007 is acknowledged. Claims 1-5, 7-12, 14 have been amended. Claim 18 has been added. Claims 1-18 are pending. Claims 15-17 are withdrawn from consideration as being drawn to a non-elected invention. Claims 1-14 and 17 are discussed in this Office action. All of the arguments have been thoroughly reviewed and considered but are not found persuasive for the reasons discussed below. Any rejection not reiterated in this action has been withdrawn as being obviated by the amendment of the claims.

This action is made FINAL.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Previous Rejections

3. The claim rejection under 35 USC 112 first paragraph as lacking enablement is maintained in part. The claim rejection under 35 USC 112 first paragraph as lacking adequate written description is withdrawn in view of Applicant's amendment. The claim rejection under 35 USC 112 second paragraph is withdrawn in part in view of Applicant's amendment of the claims. The claim rejection under 35 USC 112 second paragraph directed to claim 7 is maintained. The prior art rejection under 35 USC 102 as being anticipated by Springer et al is withdrawn in view of Applicant's amendment. The prior art rejection under 35 USC 102 as being anticipated by Dowson et al is maintained and discussed below. The prior art rejection under 35 USC 103(a) as being unpatentable over Dowson et al in view of Kell et al is maintained and discussed below.

Claim Rejections - 35 USC § 112: Enablement

4. Once again, Claims 1and 6-10 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. While the specification is enabling for the method of identifying penicillin resistance in *Streptococcus pneumoniae* using probes selected from SEQ ID NO: 7-13 and SEQ ID NO:18-19, the specification does not enable one skilled in the art to which it pertains or with which it is most nearly connected to make or use the invention commensurate in scope with the claims. There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirements and whether undue experimentation would be required to make and use the claimed invention (see *In re Wands*, 858 F. 2d 731, 737, 8 USPQ 2d 1400, 1404, 1988). These factors include but are not limited to:

Breadth of the Claims

The claims are written so broadly so as to encompass all antibiotics, a very large genus of bacteria and an enormous genus of oligonucleotide sequences i.e. SEQ ID NO: 7-13 and SEQ ID NO: 18-19 and oligonucleotides which differ therefrom by one or several nucleotides. The specification teaches a method for identifying penicillin resistance in *Streptococcus pneumoniae* comprising the step of hybridizing with penicillin resistance-specific DNA probes i.e. SEQ ID NO: 18-19, and penicillin sensitivity-specific probes i.e. SEQ ID NO: 7-13 and the specification teaches SEQ ID NO: 7-13 and SEQ ID NO: 18-19 (see pages 3 and 4) but the specification does not teach the method for identifying resistance to all antibiotics in any bacterium using the enormous species of claimed DNA probes. While the specification is enabling for the method for identifying resistance to one antibiotic, i.e. penicillin, in one bacterium i.e., *Streptococcus pneumoniae*, by hybridization with SEQ ID NO: 7-13 and SEQ ID NO:18-19, the specification is not enabling identifying resistance to all antibiotics in the large genus of bacteria using the enormous species of claimed DNA probes. Therefore, the specification is not enabling for the broadly claimed invention.

Nature of the Invention

The nature of the invention is such that identifying antibiotic resistance by hybridization with DNA probes would require a teaching of a relationship between the antibiotic resistance and the claimed DNA probes wherein the teaching would minimally include an illustration or examples of the relationship between resistance to antibiotics in a variety of bacterial species and the DNA to which the claimed DNA probes hybridize. The specification does not teach a relationship between resistance to antibiotics in bacteria and the *enormous* genus of claimed DNA probes. The specification teaches a method for identifying penicillin resistance in *Streptococcus pneumoniae* comprising the step of hybridizing with SEQ ID NO: 7-13 and SEQ ID NO: 18-19 (page 3 and 4). However, the specification does not teach the enormous genus of claimed probes i.e., any probe that may be sensitivity-specific or resistance-specific or any oligonucleotides which differ from SEQ ID NO: 7-13 and SEQ ID NO: 18-19 by one or several nucleotides; the specification does not teach identifying penicillin resistance using the enormous genus of claimed probes other than SEQ ID NO: 7-13 and 18-19; and the specification does not even suggest which, if any of the claimed DNA probes would identify resistance to antibiotics. While the specification teaches a relationship between penicillin resistance in *Streptococcus pneumoniae* and SEQ ID NO: 7-13 and SEQ ID NO: 18-19, the specification does not teach a relationship between antibiotic resistance in bacteria and the enormous genus of claimed DNA probes which would enable one of skill in the art to make and use the invention as claimed.

State of the Art

The state of the art is such that identifying antibiotic resistance in bacteria is antibiotic-specific, bacteria-specific, and gene sequence-specific as taught by Dubuc et al. (WO96/08582. 21 March 1996, page 38, Table 8). The specification teaches a method for identifying resistance to one antibiotic i.e. penicillin, in one strain of bacteria i.e. *Streptococcus pneumoniae*, using sequence-specific probes from one gene i.e. PBP comprising resistance-specific DNA probes SEQ ID NO: 18-19 and sensitivity-specific DNA probes SEQ ID NO: 7-13. Therefore, in view of the state of the prior art wherein identifying antibiotic resistance is antibiotic-specific, bacteria-specific, and gene sequence-specific, the specification does not enable one of ordinary skill in the art to make and use the invention as claimed.

Level of Predictability in the Art

The level of predictability in the art with regard to oligonucleotide hybridization using probes, which differ by one or several nucleotides, is very low. It was well know in the art at the time the claimed invention was made and the specification teaches that oligonucleotide hybridization is dependent upon complementation between the target and the probe, AT/CG content and hybridization conditions (page 6). Therefore, identification of antibiotic resistance using hybridization is dependent upon complementation between the target and the probe, AT/CG content and hybridization conditions. Because oligonucleotide probes which differ by one or several nucleotides would differ in complementation to the target and differ in AT content, hybridization using the enormous genus of claimed DNA probes may or may not identify antibiotic-specific targets and therefore may or may not identify antibiotic resistance. Therefore, because the level of predictability in the art is very low with regard to hybridization using the enormous species of claimed DNA probes, the level of predictability in the art is very low with regard to identifying antibiotic resistance in bacteria using the claimed probes.

Existence of Working Examples

The specification teaches a method for identifying penicillin resistance in *Streptococcus pneumoniae* comprising the step of hybridizing with penicillin resistance-specific DNA probes and penicillin sensitivity-specific probes and the specification teaches SEQ ID NO: 7-13 and SEQ ID NO: 18-19 and the specification teaches identification of penicillin resistance using PCR amplification. However, the specification does not teach working examples of the broadly claimed invention i.e. identifying resistance to all antibiotics in any bacterium using an enormous genus of DNA probes. Therefore, the specification does not provide working examples of the claimed invention which would enable one of ordinary skill in the art to make and use the invention as claimed.

Quantity of Experimentation Required

In view of the breadth of the claims being drawn to identifying resistance to a large genus of antibiotics in a very large genus of bacteria using an enormous genus of DNA probes; in view of the nature of the invention in which identifying antibiotic resistance in bacteria would require a teaching of a relationship between resistance to antibiotics in the large genus of bacteria and the enormous genus of claimed DNA probes and the lack of such a teaching in the specification of the relationship; in view of the state of the art in which identification of resistance to antibiotics is antibiotic-specific, bacteria-specific, and gene sequence-specific; and in view of the lack of working examples of the broadly claimed invention, it would require undue experimentation for one skilled in the art to make and use the invention as claimed.

Response to Arguments

5. Applicant traverses the rejection on the grounds that the claims are directed to testing *S. pneumoniae* for resistance to penicillin. Applicant asserts that the method include probes consisting of a discrete set of resistance -specific or sensitivity specific oligonucleotide sequences. Applicant states that the Examiner has misdirected analysis of the factors for determining enablement. Applicant states that one skilled in the art could clearly discern which sequences are specific for penicillin resistant strains an which particular mutation are spread among various penicillin resistant strains by referring the sequences depicted in Figure 4. Applicant asserts that Figure 4 provides sufficient information to select suitable probes for use according to the method of the invention to discriminate between penicillin sensitive and penicillin resistant strain including the use of probes which differ by one to four nucleotides from SEQ ID NOS: 1-19. Applicant contends that the sequences of targets of the probes are taught in Figure 4 and it would be only routine work without unpredictability for a skilled person to make a probe which hybridizes to a given sequence.

6. All of the arguments have been thoroughly reviewed and considered but are not found persuasive for the reasons that follow: In response to applicants arguments that

the claims includes probes consisting of a discrete set of resistance specific or sensitivity specific oligonucleotide sequences, it is noted that the claims as currently amendment do not recite the limitations argued by Applicant. Rather the claims required "a DNA probe that hybridizes to a DNA sequence specific for penicillin sensitive strains of *S. pneumoniae*" and "a DNA probe that hybridizes to a DNA sequence specific for penicillin resistant strains of *S. pneumoniae*". The DNA probes as recited above are not limited to any specific sequence or discrete set of resistance specific or sensitivity specific oligonucleotide sequences. On the contrary, the claims only require that the oligonucleotide sequence hybridize to a DNA sequence that is specific for penicillin resistance or specific for penicillin sensitive strains of *S. pneumoniae*. The claims are not limited to any specific DNA probe sequence and hence read on any DNA sequence that can bind to a DNA sequence that associates with penicillin sensitivity or penicillin resistance in strains of *Strep. pneumoniae,* said DNA probe sequence may or may not be effective in distinguishing between strains that are resistance to - or sensitive to penicillin. Likewise, the specification does not address the plethora of nucleic acid sequences which may bind to the different strains of S. *pneumoniae* (both antibiotic resistance and antibiotic sensitivity), but ineffective in distinguishing between the different strains, While the Examiner acknowledges the Figure 4, it is noted that the Figure 4 does not address these plethora of DNA probe sequences encompassed by the claims nor does the Figure 4 provides any evidence that any sequence which can bind to a DNA sequence from a resistance or sensitive strain of *S. pneumoniae* is capable of functioning in a method to determine penicillin

resistance. Additionally, while the examiner acknowledges the specification's teaching of specific probes which are considered penicillin-resistant specific probes (SEQ ID NO: 14-19) and penicillin-sensitive specific probes (SEQ ID NO: 1-13), the specification, in particular Figure 4, does not satisfy the enablement requirement because persons having ordinary skill in the art would not have been able to visualize and recognize the identity of the claimed probe sequences effective for distinguishing between antibiotic resistance or antibiotic sensitivity strains, without considering additional knowledge in the art, performing additional experimentation, and testing to confirm results. Thus, the Examiner maintains that the scope of the instant invention as currently written is unpredictable.

Claim Rejections - 35 USC § 112

7. Claim 7 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

(a) Claim 7 is indefinite at the recitation of "stringent conditions" because the definition at page 5 is ambiguous and it cannot be determined what hybridization conditions are required for the instant invention. It is suggested inserting the hybridization conditions into the claim.

Response to Arguments

8. Applicant asserts that the claim has been amended to recite that the hybridization occurs at 20 degrees Celsius below the melting point of the hybridizing DNA. This argument is not found persuasive because it does not address what conditions are required for the hybridization reaction to be considered stringent. For example, the claim does not recite any specific wash conditions and temperature conditions which would allow one to determine what is meant by stringent in relations to the hybridization reaction for the instant invention.

Claim Rejections - 35 USC § 102

9. Claims 1 and 6 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Dowson et al. (Proc. Natl. Acad. Sci. USA, 1990, 87: 5858-5862).

Regarding Claim 1, Dowson et al. disclose a method for identifying antibiotic resistance in bacteria comprising: isolating bacterial DNA and hybridizing the DNA with at least one sensitivity-specific DNA probe (Pn12) and at least one resistance-specific DNA probe (Pn11 and Pn13) (page 5859, right column second full paragraph), wherein the bacteria is Streptococcus pneumoniae (page 5859, right column second full paragraph) and wherein the antibiotic resistance is a penicillin resistance (Abstract and page 5859, right column second full paragraph).

Regarding Claim 6, Dowson et al. disclose the method wherein the probes are labeled radioactively (page 5859, right column, lines 4-6). Therefore, Dawson meets the limitations of the claims recited above.

Response to Argument

10. Applicant traverses the rejection on the ground that the Office has taken a primary reference that is unequivocally directed to very distinct subject matter and using impermissible hindsight attempt to reconstruct the presently claimed invention. Applicant states that Dowson et al does not teach or suggest detection of penicillin resistance in *S. pneumoniae*. Applicant asserts that the probes disclosed by Dowson et al were applied to DNA of *S. Sanguis* and *S.oralis*. Applicant further argues that Dowson et al do not disclose detection of penicillin resistance of *S. pneumonia* as resistance was already established in the tested bacteria. Applicant states that thus Dowson did not disclose whether any *S. pneumoniae* was sensitive to penicillin as recited in the claim 1.

11. All of the arguments have been thoroughly reviewed and considered but are not found persuasive for the reasons that follow: In response to applicant's argument that the examiner's rejection is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a

reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). In this case, contrary to applicant's assertion, the reference of Dowson et al do teach and suggest detection of penicillin resistance in *S. pneumoniae* by the teaching of genes found in penicillin-resistance and penicillin-sensitive strains of *S. pneumoniae* and DNA probe sequences which hybridizes to these sequences within these strains (See page 5859, col. 2 and Table 1). Therefore, this argument is not found persuasive. In regards to Applicant's arguments that the probes taught by Dowson et al were applied to DNA of *S. sanguis* and *S. oralis*, it is noted that the instant invention as currently written do not exclude the DNA probes from hybridizing to other bacterial strains, besides S. pneumoniae. Nonetheless, contrary to Applicant's assertion, Dowson et al do teach wherein the probes were used to hybridize to strains of S. pneumoniae in addition to *S. sanguis* and *S. oralis* to detect resistance and sensitive penicillin strains (see page 5859, col. 2 and last paragraph of col. 1 at page 5862). Thus, this argument is not found persuasive.

In response to Applicant's arguments that Dowson et al do not disclose detection penicillin resistance of S. pneumoniae resistance as this was already established in the test bacteria, it is noted that Applicant's arguments supports the Examiner's assertion that the claimed invention as currently rejected is not novel. Further, the Examiner maintains that the claims as broadly written are not distinct from the teachings of the prior art because Dowson et al teach the screening of strains of *S. pneumoniae* along with other viridans streptococci to determine how specific probes (penicillin resistant specific probes and penicillin sensitive specific probes) hybridize to various

Streptococcus strains (see page 5859 and 5862). Additionally, like Applicant, Dowson focuses on the hybridization properties of the probes to determine the characteristics of the bacterial strains. Applicant's argument is not found persuasive. Accordingly, the rejection is maintained.

Claim Rejections - 35 USC § 103

12. Once again, claims 2-3, 11, 12 and 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dowson et al. (Proc. Natl. Acad. Sci. USA, Aug. 1990, 87: 5858-5862) as applied to Claim 1 above and further in view of Kell et al (Infection and Immunity, vol. 61, No. 10, pages 4382-4391, 1993).

Regarding Claims 2-3, 11, 12 and 14, Dowson et al. teach a method for identifying penicillin resistance in bacteria comprising: isolating bacterial DNA and hybridizing the DNA with at least one sensitivity-specific and at least one resistance-specific probe (page 5859, right column, second full paragraph). Additionally, they teach that the PBP genes in penicillin sensitive and resistant strains of *S. pneumoniae* comprise highly conserved regions alternating with highly divergent regions (Abstract). Dowson et al. do not teach the sensitivity-specific probes are selected from SEQ ID NO: 7-13 and the resistance-specific probes are selected from SEQ ID NO: 18-19 or sequences that differ from said sequences by one to four nucleotides.

Kell et al. teach the PBP2x gene sequence of penicillin-resistant pneumococci and sequences which confer antibiotic resistance to pneumococci in patients wherein said sequence comprises the sequence of SEQ ID NO: 8 (see accession number z21803 and Figure 4). Kell et al distinguishes between sequences of pneumococci that resistant and susceptible to penicillin (see page 4388). Therefore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the PBP2x gene sequence differences between antibiotic sensitive and antibiotic resistant strains and to use probes which hybridize to those sequences in the method of Dowson et al. for identifying antibiotic resistant bacteria for the obvious benefit of identifying clinically important antibiotic-resistant bacteria efficiently and economically using DNA hybridization and antibiotic response-specific probes.

Response to Arguments

13. Applicant traverses the rejection on the ground that the Office has taken a primary reference that is unequivocally directed to very distinct subject matter and using impermissible hindsight attempt to reconstruct the presently claimed invention. Applicant states that Dowson et al does not teach or suggest detection of penicillin resistance in *S. pneumoniae*. Applicant asserts that the probes disclosed by Dowson et al were applied to DNA of *S. Sanguis* and *S.oralis*. Applicant further states that Kell et al do not overcome the shortcomings of Dowson et al to arrive at the present invention. Applicant states that Kell et al do not provide any guidance on the selection of sensitivity specific or resistance specific probes from S pneumoniae. Applicant

further states that a skilled person would not be motivated to modify Dowson et al to arrive at the present invention.

14. All of the arguments have been thoroughly reviewed and considered but are not found persuasive for the reasons that follow: In response to Applicant's arguments concerning the Dowson et al reference, the Examiner maintains that Dowson meets the limitations of the claims for the reasons discussed below. In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, the examiner maintains that Dowson et al teach a method for testing S. pneumoniae for resistance to penicillin as previously described above, but do not teach wherein the probe sequences comprises a sequence selected from SEQ ID NOS: 1-19. Kell provides the teachings not found in the Dowson et al reference. As stated in the prior Office action, Kell et al teach a sequence that is 100% identical to the sequence of SEQ ID NO: 8 and teach wherein the sequence is used to distinguish between sequences of pneumococci that is resistant and susceptible to penicillin. Further Kell et al provides motivation for using the probe sequence in the method of Dowson in the teaching that the probe sequence allows the identification of clinically important antibiotic resistant bacterial strains efficiently and economically, thus

indicating a further improvement over the teachings of Dowson. Additionally, it is noted that Kell uses the probe sequence for the same purpose as Applicant, which further substantiates its usefulness in the method of Dowson. Applicant's arguments are not found persuasive.

New Grounds of Rejections

Claim Rejections - 35 USC § 112

15. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

16. Claim 18 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. While the specification is enabling for the method of identifying penicillin resistance in *Streptococcus pneumoniae* using plurality of probes selected from SEQ ID NO: 7-13 and 18-19, the specification does not enable one skilled in the art to which it pertains or with which it is most nearly connected to make or use the invention commensurate in scope with the claims. There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirements and whether undue experimentation would be required to make and use the claimed

invention (see *In re Wands*, 858 F. 2d 731, 737, 8 USPQ 2d 1400, 1404, 1988). These factors include but are not limited to:

Breadth of the Claims

The claims are written so broadly so as to encompass all antibiotics, a very large genus of bacteria and an enormous genus of oligonucleotide sequences i.e. SEQ ID NO: 7-13 and SEQ ID NO: 18-19 and oligonucleotides which differ therefrom by one or several nucleotides. The specification teaches a method for identifying penicillin resistance in *Streptococcus pneumoniae* comprising the step of hybridizing with penicillin resistance-specific DNA probes i.e. SEQ ID NO: 18-19, and penicillin sensitivity-specific probes i.e. SEQ ID NO: 7-13 and the specification teaches SEQ ID NO: 7-13 and SEQ ID NO: 18-19 (see pages 3 and 4) but the specification does not teach the method for identifying resistance to all antibiotics in any bacterium using the enormous species of claimed DNA probes. While the specification is enabling for the method for identifying resistance to one antibiotic, i.e. penicillin, in one bacterium i.e., *Streptococcus pneumoniae*, by hybridization with SEQ ID NO: 7-13 and SEQ ID NO:18-19, the specification is not enabling identifying resistance to all antibiotics in the large genus of bacteria using the enormous species of claimed DNA probes. Therefore, the specification is not enabling for the broadly claimed invention.

Nature of the Invention

The nature of the invention is such that identifying antibiotic resistance by hybridization with DNA probes would require a teaching of a relationship between the

antibiotic resistance and the claimed DNA probes wherein the teaching would minimally include an illustration or examples of the relationship between resistance to antibiotics in a variety of bacterial species and the DNA to which the claimed DNA probes hybridize. The specification does not teach a relationship between resistance to antibiotics in bacteria and the *enormous* genus of claimed DNA probes. The specification teaches a method for identifying penicillin resistance in *Streptococcus pneumoniae* comprising the step of hybridizing with SEQ ID NO: 7-13 and SEQ ID NO: 18-19 (page 3 and 4). However, the specification does not teach the enormous genus of claimed probes i.e., any probe that may be sensitivity-specific or resistance-specific or any oligonucleotides which differ from SEQ ID NO: 7-13 and SEQ ID NO: 18-19 by one or several nucleotides; the specification does not teach identifying penicillin resistance using the enormous genus of claimed probes other than SEQ ID NO: 7-13 and 18-19; and the specification does not even suggest which, if any of the claimed DNA probes would identify resistance to antibiotics. While the specification teaches a relationship between penicillin resistance in *Streptococcus pneumoniae* and SEQ ID NO: 7-13 and SEQ ID NO: 18-19, the specification does not teach a relationship between antibiotic resistance in bacteria and the enormous genus of claimed DNA probes which would enable one of skill in the art to make and use the invention as claimed.

State of the Art

The state of the art is such that identifying antibiotic resistance in bacteria is antibiotic-specific, bacteria-specific, and gene sequence-specific as taught by Dubuc et al. (WO96/08582. 21 March 1996, page 38, Table 8). The specification teaches a method for identifying resistance to one antibiotic i.e. penicillin, in one strain of bacteria i.e. *Streptococcus pneumoniae*, using sequence-specific probes from one gene i.e. PBP comprising resistance-specific DNA probes SEQ ID NO: 18-19 and sensitivity-specific DNA probes SEQ ID NO: 7-13. Therefore, in view of the state of the prior art wherein identifying antibiotic resistance is antibiotic-specific, bacteria-specific, and gene sequence-specific, the specification does not enable one of ordinary skill in the art to make and use the invention as claimed.

Level of Predictability in the Art

The level of predictability in the art with regard to oligonucleotide hybridization using probes, which differ by one or several nucleotides, is very low. It was well know in the art at the time the claimed invention was made and the specification teaches that oligonucleotide hybridization is dependent upon complementation between the target and the probe, AT/CG content and hybridization conditions (page 6). Therefore, identification of antibiotic resistance using hybridization is dependent upon complementation between the target and the probe, AT/CG content and hybridization conditions. Because oligonucleotide probes which differ by one or several nucleotides would differ in complementation to the target and differ in AT content, hybridization

using the enormous genus of claimed DNA probes may or may not identify antibiotic-specific targets and therefore may or may not identify antibiotic resistance. Therefore, because the level of predictability in the art is very low with regard to hybridization using the enormous species of claimed DNA probes, the level of predictability in the art is very low with regard to identifying antibiotic resistance in bacteria using the claimed probes.

Existence of Working Examples

The specification teaches a method for identifying penicillin resistance in *Streptococcus pneumoniae* comprising the step of hybridizing with penicillin resistance-specific DNA probes and penicillin sensitivity-specific probes and the specification teaches SEQ ID NO: 7-13 and SEQ ID NO: 18-19 and the specification teaches identification of penicillin resistance using PCR amplification. However, the specification does not teach working examples of the broadly claimed invention i.e. identifying resistance to all antibiotics in any bacterium using an enormous genus of DNA probes. Therefore, the specification does not provide working examples of the claimed invention which would enable one of ordinary skill in the art to make and use the invention as claimed.

Quantity of Experimentation Required

In view of the breadth of the claims being drawn to identifying resistance to a large genus of antibiotics in a very large genus of bacteria using an enormous genus of DNA probes; in view of the nature of the invention in which identifying antibiotic resistance in bacteria would require a teaching of a relationship between resistance to antibiotics in

the large genus of bacteria and the enormous genus of claimed DNA probes and the lack of such a teaching in the specification of the relationship; in view of the state of the art in which identification of resistance to antibiotics is antibiotic-specific, bacteria-specific, and gene sequence-specific; and in view of the lack of working examples of the broadly claimed invention, it would require undue experimentation for one skilled in the art to make and use the invention as claimed.

Claim Rejections - 35 USC § 112

17. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

18. Claim 7 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

(a) The claim 7 is confusing at lacks proper antecedent basis for the "the melting point of the hybridizing DNA" because the claim 1 from which the claim depends does not recite any melting temperature or recite a hybridizing DNA. Clarification is required.

Prior art

20. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Zhang et al teach a method for testing *S. pneumoniae*, the method comprising isolating DNA from *S. pneumoniae*, hybridizing the DNA with a plurality of DNA probes that hybridizes to a DNA sequence from *S. pneumoniae*

irregardless to whether the S. pneumoniae is penicillin resistance or penicillin sensitive. Zhang et al do not teach determining whether or not the strains of *S. pneumoniae* are resistance or sensitive to antibiotic treatment.

Conclusion

21. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Cynthia B. Wilder, Ph.D. whose telephone number is (571) 272-0791. The examiner can normally be reached on a flexible schedule.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

cbw

GARY BENZION, PH.D
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600